Clinical trial results:
A Randomised, Double-Blind Phase II Trial of Topical HDIT101 versus Placebo in Patients with Chronic Recurrent HSV-1 Infection and Orolabial Lesion

Summary

EudraCT number	2020-000926-24
Trial protocol	DE AT
Global end of trial date	31 May 2023

Results information

Result version number	v1 (current)
This version publication date	13 June 2024
First version publication date	13 June 2024

Trial information

Trial identification

Sponsor protocol code	HTX101-03L

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04539483
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Heidelberg ImmunoTherapeutics
Sponsor organisation address	Max-Jarecki-Str. 21, Heidelberg, Germany, 69115
Public contact	Dr. Michaela Arndt, Heidelberg ImmunoTherapeutics, michaela.arndt@hditx.de
Scientific contact	Dr. Michaela Arndt, Heidelberg ImmunoTherapeutics, michaela.arndt@hditx.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2023
Global end of trial reached?	Yes
Global end of trial date	31 May 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical efficacy of topical HDIT101 in patients with chronic recurrent orolabial HSV-1 infection and at least 6 lesion outbreaks/year by comparing the number of recurrences of orolabial lesions for 12 months after topical administration of HDIT101/placebo.

Following the treatment phase of the first 55 patients, an interim analysis was conducted per protocol by an unblinded expert panel. This analysis, carried out on March 9, 2023, recommended premature termination of the study due to futility in achieving the primary endpoint. A thorough analysis excluded any possible systemic error, therefore, on April 27, 2023, the decision was made to prematurely terminate MATCH-1, stop IMP allocation and end all ongoing patients until May 31, 2023.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. The subjects were allowed to use topical aciclovir for all recurrences except the two recurrences treated with HDIT101/placebo.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 158
Worldwide total number of subjects	158
EEA total number of subjects	158

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	157
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with a history of at least 12 months of chronic recurrent orolabial HSV-1 infection with ≥ 6 outbreaks in the last year were eligible for enrolment in this study.

Pre-assignment

Screening details:

Eligible patients entered observation/screening phase of max 9 months. Patients must have had 3 recurrences within the observation phase, Randomisation / treatment took place upon occurrence of the third lesion. Patients who did not develop 3 recurrences in 9 months (or first recurrence 150 days after enrollment) were considered screening failures.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	HDIT101

Arm description:

Topical application of HDIT101

Arm type	Experimental
Investigational medicinal product name	HDIT101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous liquid
Routes of administration	Topical use

Dosage and administration details:

A humanised monoclonal antibody (mAb) against herpes simplex virus (HSV) type 1 and 2 surface glycoprotein B (gB) locally administered two times daily for two consecutive days (4x one vial containing 500 µl, each 5 mg/mL) upon ≥ 3 (and ≤ 4) grade lesion outbreak. A maximum of 2 outbreaks were treated (i.e. max. 8 applications per patient).

Arm title	Placebo

Arm description:

Topical application of Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous liquid
Routes of administration	Topical use

Dosage and administration details:

Placebo consisted of the formulation buffer of HDIT101 and was identical in appearance to verum. Placebo was also locally administered two times daily for two consecutive days upon ≥ 3 grade lesion outbreak. A maximum of 2 outbreaks were treated (i.e. max. 8 applications per patient)

Number of subjects in period 1	HDIT101	Placebo
Started	104	54
Completed	58	31
Not completed	46	23
Consent withdrawn by subject	4	1
Lost to follow-up	1	1
Premature termination of trial	41	21

Baseline characteristics

Reporting groups	
Reporting group title	HDIT101
Reporting group description:	
Topical application of HDIT101	
Reporting group title	Placebo
Reporting group description:	
Topical application of Placebo	

Reporting group values	HDIT101	Placebo	Total
Number of subjects	104	54	158
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	36.3	34.7	
standard deviation	± 11.6	± 11.2	-
Gender categorical			
Units: Subjects			
Female	83	41	124
Male	21	13	34
BMI			
Body mass index (mean)			
Units: kg/m2			
arithmetic mean	24.85	23.31	
standard deviation	± 4.23	± 2.96	-
Time from onset of orolabial herpes			
Units: years			
arithmetic mean	24.11	22.77	
standard deviation	± 11.85	± 12.11	-
Number of episodes in the last 12 months			
Units: recurrence			
arithmetic mean	8.86	8.37	
standard deviation	± 3.86	± 2.37	-

End points

End points reporting groups	
Reporting group title	HDIT101
Reporting group description: Topical application of HDIT101	
Reporting group title	Placebo
Reporting group description: Topical application of Placebo	

Primary: Primary: Recurrence of lesions	
End point title	Primary: Recurrence of lesions
End point description: Number of recurrences after topical HDIT101 versus placebo after 12 months. A lesion was considered as such, if rated 3-7 according the HSV lesion score (grade 2 was rated as “aborted lesion”). The recurrence rate was defined as number of recurrences in the 12 months treatment phase divided by the total number of study days (in the 12 months treatment phase) after IMP treatment for lesion 3.	
End point type	Primary
End point timeframe: 12 months from start of treatment	

End point values	HDIT101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	54		
Units: Number of Recurrences				
arithmetic mean (standard deviation)	3.1 (± 2.4)	2.3 (± 1.8)		

Statistical analyses

Statistical analysis title	Treatment contrast
Statistical analysis description: The contrast between both treatment groups estimating the rate ratio as ratio of number of recurrences rHDIT101 / rplacebo adjusted for total days in study, with lower values in favour of HDIT101 -Wald z-statistic, one-sided p-value and the associated Wald CI was analyzed. The significance level set to 2.5% (one-sided,), the corresponding level of one-sided (upper) CI was 97.5%	
Comparison groups	HDIT101 v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9934
Method	Wald z-statistic
Parameter estimate	event rate ratio
Point estimate	1.442

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.93

Secondary: Key Secondary 1 - Percentage of days with a lesion

End point title	Key Secondary 1 - Percentage of days with a lesion

End point description:

Percentage of days with a lesion in the 12 months treatment period.

End point type	Secondary

End point timeframe:

12 months after start of treatment

End point values	HDIT101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	54		
Units: percent				
arithmetic mean (standard deviation)	13.9 (± 9.2)	11.7 (± 8.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Key Secondary 2 - Recurrence Duration

End point title	Key Secondary 2 - Recurrence Duration

End point description:

Mean duration of recurrent lesions (calculated as consecutive days with lesions of HSV score ≥ 3-7).

End point type	Secondary

End point timeframe:

12 month after start of treatment

End point values	HDIT101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	54		
Units: Days				
arithmetic mean (standard deviation)	8.23 (± 5.99)	7.54 (± 5.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Key Secondary 3: Time to first recurrence

End point title	Key Secondary 3: Time to first recurrence

End point description:

Time to first recurrence of lesion (= lesion no. 4; HSV lesion score must be 3-7) reported by the patient and verified by the investigator.

End point type	Secondary

End point timeframe:

12 months after start of treatment

End point values	HDIT101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	54		
Units: Days				
median (inter-quartile range (Q1-Q3))	67.0 (36.5 to 129.0)	101.0 (38.0 to 204.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were recorded throughout the study from FPI - Early termination of the study (01-Oct-2020 - 31-May-2023)

Adverse event reporting additional description:

The analysis of AEs focused on TEAEs (defined as all AEs that started or worsened after first treatment with IMP) and were performed by primary MedDRA SOC and PT. Patients were counted only once if they had more than one TEAE within a SOC or experienced a preferred term more than once.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	HDIT101

Reporting group description:

Topical application of HDIT101

Reporting group title	Placebo

Reporting group description:

Topical application of Placebo

Serious adverse events	HDIT101	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 104 (0.00%)	0 / 54 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	HDIT101	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 104 (25.00%)	11 / 54 (20.37%)	
Cardiac disorders			
Cardiac disorder	Additional description: All		
subjects affected / exposed	0 / 104 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Surgical and medical procedures			
surgical and medical procedures	Additional description: All		

subjects affected / exposed	1 / 104 (0.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Nervous system disorder	Additional description: All		
subjects affected / exposed	5 / 104 (4.81%)	1 / 54 (1.85%)	
occurrences (all)	6	1	
General disorders and administration site conditions			
General Disorder	Additional description: All		
subjects affected / exposed	3 / 104 (2.88%)	0 / 54 (0.00%)	
occurrences (all)	5	0	
Immune system disorders			
Immune system disorder	Additional description: All		
subjects affected / exposed	1 / 104 (0.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All		
subjects affected / exposed	4 / 104 (3.85%)	1 / 54 (1.85%)	
occurrences (all)	4	1	
Reproductive system and breast disorders			
Reproductive system and breast disorders	Additional description: All		
subjects affected / exposed	1 / 104 (0.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All		
subjects affected / exposed	1 / 104 (0.96%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Renal and urinary disorders	Additional description: All		
subjects affected / exposed	1 / 104 (0.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: All		
subjects affected / exposed	1 / 104 (0.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

infections and infestations	Additional description: All		
subjects affected / exposed	13 / 104 (12.50%)	6 / 54 (11.11%)	
occurrences (all)	14	9	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders	Additional description: All		
subjects affected / exposed	1 / 104 (0.96%)	1 / 54 (1.85%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2020	Section 12.8: Criteria for Premature Termination were added as requested from the Competent Authority Change in address of Coordinating investigator Additional minor correction of typos, changes in wording or other minor clarifications/changes.
15 April 2021	Screening phase criteria were updated (1 lesion within 150 day required) Several inclusion and exclusion criteria were specified or adapted contraception methods were updated Paracetamol and ibuprofen were allowed as concomitant medication Documentation of lesion score and aborted lesion definition was specified in more detail Study timelines updated Sponsor address updated Additional minor correction of typos, changes in wording or other minor clarifications/changes.
28 June 2022	Number of sites was increased Endpoint definitions were specified Country specific text for Austria included Timelines were updated Minor changes and corrections

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The DMC recommended to terminate the study early due to futility. There were no safety concerns. Due to the early termination, not all planned analyses could be or have been performed, therefore only key outcome and safety results are reported.

Notes: